

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/26610

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/68; C07H 21/04
US CL : 435/6; 536/23.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6; 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	RUTTER et al. A Single Nucleotide Polymorphism in the Matrix Metalloproteinase-1 Promoter Creates an Ets Binding Site and Augments Transcription. Cancer Research. 01 December 1998, Bol. 58, pages 5321-5325, see entire document.	1-5
A	WESTERMARCK et al. Differential regulation of interstitial collagenase (MMP-1) gene expression by ETS transcription factors. Oncogene. 1997, Vol. 14, pages 2651-2660.	1-5
A	LOGAN et al. Synergistic Transcriptional Activation of the Tissue Inhibitor of Metalloproteinases-1 Promoter via Functional Interaction of AP-1 and Ets-1 Transcription Factors. 12 January 1996, Vol. 271, No. 2, pages 774-782.	1-5
A	WHITE et al. ETS Sites in the Promoters of the Matrix Metalloproteinases Collagenase (MMP-1) Stromelysin (MMP-3) are Auxiliary Elements that Regulate Basal and Phorbol-Induced Transcription. Connective Tissue Research. 1997, Vol. 36, No. 4, pages 321-335.	1-5
A	US 5,744,442 A (RICHARDS et al.) 28 April 1998 (28.04.1998), see entire document.	1-5

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

08 February 2000 (08.02.2000)

Date of mailing of the international search report

15 MAR 2000

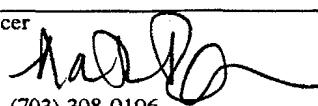
Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Faxsimile No. (703) 305-3230

Authorized officer

Gary Jones



Telephone No. (703) 308-0196

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
JANE MASSEY LICATA
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON, NJ 08053

Priority System

NP - 5/30/01

Applicant's or agent's file reference

DC-0120

International application No.

PCT/US99/26610

Applicant

TRUSTEES OF DARTMOUTH COLLEGE

PCT
NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing
(day/month/year)

11 APR 2001

IMPORTANT NOTIFICATION

Priority date (day/month/year)

30 November 1998 (30.11.1998)

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703)305-3230

Form PCT/IPEA/416 (July 1992)

Authorized officer
Jeanine Enewold Goldber

Telephone No. (703) 308-0196

TERRY J. DEY
PARALEGAL SPECIALIST
TECHNOLOGY CENTER 1600

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference DC-0120	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/26610	International filing date (day/month/year) 10 November 1999 (10.11.1999)	Priority date (day/month/year) 30 November 1998 (30.11.1998)

International Patent Classification (IPC) or national classification and IPC
IPC(7): C12Q 1/68; C07H 21/04 and US Cl.: 435/6; 536/23.1
Applicant
TRUSTEES OF DARTMOUTH COLLEGE

<ol style="list-style-type: none"> This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. This REPORT consists of a total of <u>4</u> sheets, including this cover sheet. <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of <u>0</u> sheets.</p>
<ol style="list-style-type: none"> This report contains indications relating to the following items: <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of report with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Jeanine Enewold Goldberg <i>[Signature]</i> TERRY J. DEY PARALEGAL SPECIALIST TECHNOLOGY CENTER 1600 Telephone No. (703) 308-0466

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/26610

I. Basis of the report

1. With regard to the elements of the international application:*



the international application as originally filed.



the description:

pages 1-13 as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of _____



the claims:

pages 14 as originally filed

pages NONE, as amended (together with any statement) under Article 19

pages NONE, filed with the demand

pages NONE, filed with the letter of _____



the drawings:

pages NONE, as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of _____



the sequence listing part of the description:

pages 1-5 as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:



the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).



the language of publication of the international application (under Rule 48.3(b)).



the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:



contained in the international application in printed form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of: the description, pages none the claims, Nos. none the drawings, sheets/fig none5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Internal application No.

S99/26610

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. STATEMENT**

Novelty (N)	Claims 1-5	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 1-5	YES
	Claims NONE	NO
Industrial Applicability (IA)	Claims 1-5	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS (Rule 70.7)

Claims 1-5 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest a method of diagnosing a matrix metalloproteinase-1 related disease in a patient comprising detecting in the patient matrix metalloproteinase-1 containing the Ets transcription factor binding site single nucleotide polymorphism.

----- NEW CITATIONS -----

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 1-5 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 5.1(a) for the reasons set forth in the immediately preceding paragraph.

The claims are broadly drawn to a method of diagnosing or prognosticating a matrix metalloproteinase-1 related disease by detecting the matrix metalloproteinase-1 (MMP-1) containing the Ets transcription factor binding site single nucleotide polymorphism. The claims are also drawn to methods of identifying therapeutic agents for treatment of a MMP-1 related disease.

The specification teaches MMP-1 is associated with irreversible degradation of cartilage, tendon and bone in arthritis, degradation of collagenase I and III in tumor invasion and metastasis (pg. 1). Furthermore, the specification teaches that patients with tumors that express MMP-1 have a poor prognosis than patients with tumors that do not express this protein (pg. 2). The specification teaches that the full length DNA sequence with only 1 G at position -1607 constitutes a SNP (pg. 3). The specification teaches that while the SNP is not located in the coding region and does not alter the structure of the enzyme, it has profound effect on the production/regulation of the enzyme (pg. 4). The specification further teaches a study in which 100 hundred control DNA's were sampled to determine the frequency of the variation in the population (pg. 8). The specification teaches that the frequency of the 2G homozygotes in the controls was approximately 30% whereas the frequency in tumor cell lines was 62.5% ($p < 0.0001$) (pg. 8). The specification provides several explanations which may explain the differences in expression such as growth factor and cytokines, specific nuclear factors within the cell (pg. 9).

The art teaches the a DNA sequence of the MMP-1 which only contained 1G at position -1607 (Rutter et al. J. Cell Biochem. 66: 322-336, 1997)(pg. 2). The art also teaches the sequence where 2Gs are located at this position (pg. 2). The consensus sequence for a functional PEA3/EBS is provided in Graves (J.B. Science 279: 1000-1001, 1998).

It would be undue experimentation for the skilled artisan to practice the invention as broadly as claimed. The assertion that the MMP-1 EBS-SNP in patients is indicative of the patient suffering from a disease relating to overexpression of the MMP-1 enzyme is not supported by any clinical studies that provide this correlation. While the specification teaches that the frequency of the 2G homozygotes is expressed more frequently in tumor cell lines, this does not provide enablement for a method of diagnosing a MMP-1 related disease based upon the identification of the SNP. The study does not provide any data taken from patients with MMP-1 diseases, but rather amorphous cell lines. Cell lines are not representative of individuals with MMP-1 related diseases. Secondly, the specification does not identify any specific disease which have been shown to be associated with the 2G polymorphism in the MMP-1. It would be undue experimentation for the skilled artisan to perform clinical studies to associate the single nucleotide polymorphism with a MMP-1 related disease. Additionally, the specification provides several plausible explanations as to the difference in expression. Thus, it is unpredictable whether the 2G polymorphism is associated with MMP-1 diseases or whether extrinsic factors affect the expression and disease characteristics.

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
 United States Patent and Trademark
 Office
 Box PCT
 Washington, D.C.20231
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 11 September 2000 (11.09.00)	
International application No. PCT/US99/26610	Applicant's or agent's file reference DC-0120
International filing date (day/month/year) 10 November 1999 (10.11.99)	Priority date (day/month/year) 30 November 1998 (30.11.98)
Applicant BRINCKERHOFF, Constance, E. et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

07 June 2000 (07.06.00)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

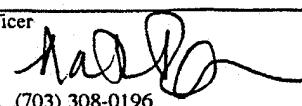
made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Charlotte ENGER Telephone No.: (41-22) 338.83.38
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/26610

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IPC(7) : C12Q 1/68; C07H 21/04 US CL : 435/6; 536/23.1		
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	RUTTER et al. A Single Nucleotide Polymorphism in the Matrix Metalloproteinase-1 Promoter Creates an Ets Binding Site and Augments Transcription. <i>Cancer Research</i> . 01 December 1998, Bol. 58, pages 5321-5325, see entire document.	1-5
A	WESTERMARCK et al. Differential regulation of interstitial collagenase (MMP-1) gene expression by ETS transcription factors. <i>Oncogene</i> . 1997, Vol. 14, pages 2651-2660.	1-5
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A	WHITE et al. ETS Sites in the Promoters of the Matrix Metalloproteinases Collagenase (MMP-1) Stromelysin (MMP-3) are Auxiliary Elements that Regulate Basal and Phorbol-Induced Transcription. <i>Connective Tissue Research</i> . 1997, Vol. 36, No. 4, pages 321-335.	1-5
A	US 5,744,442 A (RICHARDS et al.) 28 April 1998 (28.04.1998), see entire document.	1-5
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/>		See patent family annex.
<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>		<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>
Date of the actual completion of the international search 08 February 2000 (08.02.2000)	Date of mailing of the international search report 15 MAR 2000	
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	<p>Authorized officer Gary Jones </p> <p>Telephone No. (703) 308-0196</p>	